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| (21) International Application Number: PCT/IL99/00365 (22) International Filing Date: 6 July 1999 (06.07.99) (30) Priority Data: 125244 7 July 1998 (07.07.98) IL (71) Applicant (for all designated States except US): YISSUM RESEARCH DEVELOPING COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM [IL/IL]; Jabotinsky Street 46, 91042 Jerusalem (IL). (71)(72) Applicant and Inventor: SINTOV, Amnon [IL/IL]; Oren Street 27, 84965 Omer (IL). (72) Inventors; and (75) Inventors/Applicants (for US only): VOLOSOV, Andrew [IL/IL]; Haarazim 21/14, 96181 Jerusalem (IL). BIALER, Meir [IL/IL]; Hahalutz Street 36, 96222 Jerusalem (IL). YAGEN, Boris [IL/IL]; Apt. 25, Neve Sheanan St. 18, 93707 Jerusalem (IL). (74) Agent: NOAM, Meir; P.O. Box 34335, 91342 Jerusalem (IL). | | (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> |
| (54) Title: PHARMACEUTICAL COMPOSITIONS CONTAINING LOW-MELTING WAXES | | |
| (57) Abstract <p>The present invention relates to pharmaceutical composition for oral administration comprising at least one active ingredient, and a low-melting wax or waxes of 30 °C to 40 °C melting point. The novel formulation is preferably applied as tablets or microspheres, providing an effective and easy mode of delivery for especially high drug-loaded systems. The composition has been found to exhibit unexpectedly enhanced drug absorption. The compositions of the present invention can further comprise any binder, glidant, lubricating compound, surfactant or any other excipients commonly-used in the art. The present invention is particularly useful for: (a) administration of less amount of drug than is required by the conventional methods while still maintaining the same activity; (b) loading more drug in smaller dispensing system; (c) a sustained drug release wherein the required rate of drug release is obtained by the percent of wax present in the composition or by combination of waxes with different melting points, all of them, or at least one of them, in the range of 30° to 40°; (d) protecting low pH-sensitive molecules in the gastric fluid and protecting proteins and peptide drugs from being degraded by the proteolytic enzymes in the intestinal lumen.</p> | | |

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PHARMACEUTICAL COMPOSITIONS CONTAINING LOW-MELTING WAXES

FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions for oral administration comprising any active ingredient and any low-melting wax of melting point in the range of 30° to 40°. The novel compositions exhibit unexpectedly enhanced drug absorption, thus, are useful to enhance gastric and intestinal absorption and providing an effective and easy mode of delivery for high drug-loaded systems. The said compositions exhibit controlled drug release wherein the control of the release rate is achieved by use of waxes with slightly different melting ranges. The said composition are also useful for protecting low pH-sensitive molecules in the gastric fluid, or for protecting proteins and peptide drugs from being degraded by the proteolytic enzymes in the intestinal lumen. The said novel compositions are preferably applied as tablets or microparticulate systems,.

BACKGROUND OF THE INVENTION

The present invention relates to pharmaceutical compositions for oral controlled delivery and sustained drug release. These compositions can be any pharmaceutically accepted systems containing any active ingredient and characterized by a low-melting wax, or combination of such waxes, as excipients. More particularly, these compositions can be compressed tablets or particulate systems that assist in binding or coating the active material, and facilitate its penetration through the lipophilic strata of the intestinal mucosa at physiological temperature.

The term "controlled release", i.e., the release of an active agent in a controlled way over a predetermined period of time, has been the subject for considerable research over the past 30 years. The ultimate goal of controlled

drug release is to achieve optimization of drug use. Controlled release can be achieved by controlling the delivery rate for longer time (sustained release) or, on the other hand, by absorption enhancement, i.e. by delivering the intact drug as quickly as possible, to provide an immediate effect. Controlled release can also be achieved by control over the location of the drug (i.e., spatial placement in the body).

Examples of systems that utilize oral controlled release of an active agent are: Microcapsules containing drugs as described in US 3242051 and US 3041289; Osmotic systems comprising a semipermeable wall that surrounds the drug as disclosed in US 3845770, US 3916899 and US 4327725; A sustained release compressed tablet based on hydrophilic gum that hydrates rapidly and swells in a physiologic fluid at body temperature, as described in US 3065143; Acrylic acid polymers in tablets as disclosed in US 3330729 and US 2798053 and controlled release systems based on copolymers of methacrylic acid and maleic anhydride as described in US 3551556.

Relatively high melting waxes, i.e., beeswax, have already been used in the microparticulate technology. Kagadis and Choulis (*Farmazie*, 40:807-808, 1985) prepared ibuprofen microcapsules from stearic acid wax. Benita *et al.* (*J. Pharm. Sci.*, 75:847-851, 1986) utilized the same methodology to prepare 5-fluorouracil microspheres from carnauba wax. Adeyeye and Price (*Pharm. Res.*, 8:1377-1383, 1991) developed ibuprofen-wax microspheres utilizing beeswax, ceresine, ozokerite, and microcrystalline wax having melting points of 64, 73, 84, and 94°C, respectively.

Based on the art, one could not have predicted that low-melting waxes would have a beneficial effect over the high-melting waxes with respect to their controlled release properties. Furthermore, one could have considered that at

body temperature the low-melting waxes would lose their matrix structure resulting in a more diffuse system with an immediate release properties.

The present invention demonstrates that incorporating these types of waxes into tablet formulations containing antiepileptic agent as a model drug, can significantly enhance the drug absorption rate and extent, as well as its elimination half-life ($t_{1/2_{kel}}$ or $t_{1/2_{10}}$).

SUMMARY OF THE INVENTION

The pharmaceutical compositions of the present invention comprise an effective amount of:

- (a) at least one orally-used or potentially orally-used active ingredient;
- (b) solid lipoids, namely glycerides of long-chain fatty acids, or any other pharmaceutically acceptable low-melting wax of melting point in the range of 30° to 40°.
- (c) In addition to (a) and (b) the composition may optionally contain any binder, glidant, lubricating compound, surfactant or any other excipients commonly-used in the art, or any combination of such materials.

In this invention low-melting waxes (30°C-40°C) at concentrations from 0.1% to 80% by weight are incorporated into pharmaceutically acceptable solid dosage forms such as tablets, capsules, microcapsules, and dragees. The waxes of the present invention are preferably selected from the series of Wittepsol (Dynamit Nobel, Hüls) which are hard fats (USP/NF) based on glycerides of saturated fatty acids.

The present invention is particularly useful for :

- (a) administration of less amount of drug than is required by the conventional methods while still maintaining the same activity, because of gastric and intestinal absorption enhancement.
- (b) loading more drug in smaller dispensing system (i.e., small tablet's size)

(c) a sustained drug release wherein the required rate of drug release is obtained by the percent of wax present in the composition or by combination of waxes with different melting points, all of them, or at least one of them, in the range of 30° to 40°.

(d) protecting low pH-sensitive molecules in the gastric fluid and protecting proteins and peptide drugs from being degraded by the proteolytic enzymes in the intestinal lumen. It should be noted that these kind of protection can allow targeting of drugs to the colon for treating colon-specific diseases or slow-release absorption in this organ.

DETAILED DESCRIPTION OF THE INVENTION

The compositions of the present invention comprise a safe and effective amount of:

- (a) at least one orally-used or potentially orally-used active ingredient, where the term active ingredient means any drug, combination of drugs or any bioactive material;
- (b) solid lipoids, namely glycerides of long-chain fatty acids, or any other pharmaceutically acceptable low-melting wax
- (c) In case where the composition is applied as a tablet: binders, glidants, lubricating compounds and other excipients commonly used in the art may be added .

In case where the composition according to the invention is a microparticulate system, any effective surfactant that is added during the preparations in order to control the particle size distribution, may be added.

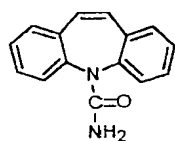
The said compositions may be applied as tablets or microparticulate systems and may be prepared by direct compression, by granulation processes, by microencapsulation, or by any technique known in the art.

The following in-vitro and in-vivo examples demonstrate the invention:

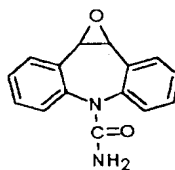
All percentages herein are by weight unless otherwise specified.

Background to Experiments

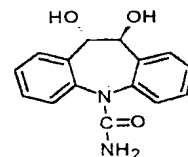
Carbamazepine-10,11-epoxide (CBZ-E) is known as a pharmacologically active metabolite of carbamazepine (CBZ), representing the major metabolic pathway of CBZ (B.M. Kerr and R.H. Levy. Carbamazepine epoxide. In: *Antiepileptic drugs*, 4th ed. Raven Press, New York, 1995). CBZ undergoes epoxidation to CBZ-E, which is subsequently converted into CBZ trans-10,11-diol by an epoxide hydrolase promoted hydrolysis (M. Eichelbaum et al. *Clinical Pharmacokinet.* 10, 80-90 (1985).). Another potential agent that also needs a better drug delivery system for optimal performance in the gastrointestinal tract is monohydroxycarbamazepine (MHD), an active metabolite (active entity) of a new antiepileptic drug, oxcarbazepine (OXC) :



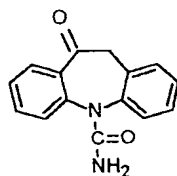
Carbamazepine
(CBZ)



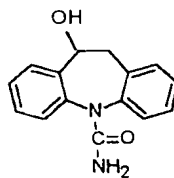
Carbamazepine-10,11-epoxide
(CBZ-E)



CBZ trans-10,11-diol



Oxcarbazepine
(OXC)



10-hydroxycarbamazepine
(MHD)

An anticonvulsant activity of CBZ-E in animals is well-established and there have been numerous investigations concerning the contribution of CBZ-E to the activity of the parent compound, CBZ. However, investigations based on

simultaneous determination of plasma levels of both compounds after CBZ administration (in a single or multiple dosing) have not been able to supply a clear-cut answer concerning the question whether and to what extent CBZ-E contributes to the clinical effects of carbamazepine. Only direct administration can provide an unequivocal evaluation of pharmacological effects of CBZ-E. Several preliminary investigations were carried out (T. Tomson et al *Arch. Neurol.* 47, 888-892, (1990)). However, formulation problems resulting in significant fluctuations in plasma levels and sometimes inconsistency of peak concentrations with the time of dosing, interfered with the evaluation of the antiepileptic potency and side effects of CBZ-E in humans. An additional complication was the fact that CBZ-E underwent decomposition in gastric juice.

In summary, the preliminary data published to date suggest that in order to conduct a reliable and rigorous evaluation of the *in vivo* performance (pharmacokinetics and pharmacodynamics) of CBZ-E, a development of an enteric-coated sustained release (SR) formulation of the drug is needed.

The approach taken in the present invention is utilizing low-melting waxes for the development of sustained-release formulations of CBZ-E.

The rationale for this decision is as follows:

- a) Preparation of formulations containing relatively small amounts (e.g., 20-30% of the tablet weight) of inactive ingredients in order to enable higher doses in one (SR) tablet;
- b) Controlling the release of CBZ-E by using various waxes with slightly different melting ranges, around the normal body temperature;
- c) The general novelty of this approach, which is based on the idea that the formulation eventually melts following oral administration, with a wide spectrum of release rates due to the difference in the melting ranges.

Example 1: In-Vitro Studies with Carbamazepine Epoxide (CBZ-E)**1.1 Materials and Methods**

- (a) CBZ-E was synthesized according to a procedure described in the literature (G. Bellucci et al. *J. Med. Chem.* 30, 768-773, (1987).), by epoxidation of CBZ with m-chloroperoxybenzoic acid. The yield of the process was about 60% (which was very close to the highest yield reported in ref. 8 for this procedure). Purified CBZ-E is a white crystalline compound with the empirical formula $C_{15}H_{12}N_2O_2$, a molecular weight of 252.27 and a melting point with decomposition at 200°C to 205°C. The final product (about 200g) obtained in our synthesis, was identified and analyzed by elemental microanalysis, IR spectrum, TLC, HPLC and melting point. The product appeared to be pure (mass balance 100.05% in the microanalysis), the melting point (with decomposition) was about 205°C.
- (b) Five Witepsol wax types (H5, H15, H37, H175 and W31, see page 9 for details) were chosen for this study. All of them had the melting range close to the body temperature and all of them represented conventional suppository bases, approved for clinical use. Witepsol is described in pharmacopoeia as hard fat based on glycerides of saturated C_{12} - C_{18} fatty acids. It is chemically and physically stable, broadly compatible with nearly all active compounds, neutral towards mucous membranes and has favorable processing properties.
- (c) The dissolution rates were determined by a conventional USP dissolution apparatus (Caleva). The standard dissolution conditions were as follows: 1000ml of distilled and degassed water, stirred with paddles at 50rpm. The temperature of the dissolution medium was 37°C, unless otherwise specified in text. Aliquots were taken manually in specified time intervals and the CBZ-E concentration was determined by HPLC.

1.2 Results

1.2a Preliminary Experiments

(a) The first experiments were carried out in order to determine whether there was a substantial difference in the release (dissolution) rate of CBZ-E powder compared to that of the powder mixed with the wax. The preparation procedure for the powder-wax formulation was as follows: CBZ-E powder was dispersed in the Witepsol H15 melted wax at about 60°C in proportion 1:1 (w/w), mixed thoroughly, the mixture was poured into a gelatin capsule, solidified and the mold obtained was removed from the capsule. Dissolution of CBZ-E powder alone was performed after the powder was placed into a conventional gelatin capsules.

In these first experiments the dissolution conditions were varied (see Table. 1) in order to determine the most suitable procedure. After that, the standard conditions were set as specified in Materials and Methods.

The results obtained (as summarized in Fig.1 and Tab.1) clearly show a very significant difference both in the release rate and the release profile, namely, the dissolution rate of the wax-containing formulation was much slower than that of the powder.

(b) The next step was to determine whether and to what extent the amount of wax in the formulation affects the dissolution rate.

At this stage, it was decided to work with more pharmaceutically acceptable oral dosage forms. Therefore, compressed tablets of CBZ-E - wax mixture instead of molds were prepared. Tablets loaded with 60%, 66%, 70%, 75% and 80% of CBZ-E (w/w) were formulated by mixing Witepsol H15 with CBZ-E at approx. 60°C. The mixture was cooled to solidification, ground and the obtained granulate was compressed into tablets.

Interestingly, tablets containing more than two thirds (>70%) of CBZ-E did not liquify at 37°C, keeping its tablet form throughout the experiment. This fact proved to be very important for further investigation, providing an opportunity

for more explicit evaluation of differences between the waxes, with respect to their influence on a release rate and also helping to determine the mechanism of release.

The experiments showed that in all cases the release rate was relatively slow (about 50% dissolved after twelve hours) and there was no significant difference between tablets containing around 80% (75%-85%) of CBZ-E. In light of these results it was decided to set the 80/20 ratio (w/w) between CBZ-E and a wax as a standard for further preparations.

1.2b INFLUENCE OF A WAX TYPE ON THE RELEASE RATE

At this stage a series of tests was carried out in order to determine the influence of a wax melting range on a release rate. As has been noted, five wax types were used:

| Wax type | Melting range (°C) |
|---------------|--------------------|
| Witepsol H37 | 36-38 |
| Witepsol W31 | 35-37 |
| Witepsol H175 | 34.5-36.5 |
| Witepsol H5 | 34-36 |
| Witepsol H15 | 33.5-35.5 |

Two types of experiments were carried out - one with molds (CBZ-E - wax 50/50 w/w) prepared as described earlier and the other with CBZ-E - wax (80/20 w/w) compressed tablets.

In both cases there was a dramatic difference in the release rates for different wax types (Figs. 2 and 3). Waxes with higher melting range caused much slower release rates than those with lower melting temperatures.

The two important conclusions drawn from these experiments were:

- (a) It was possible to control the release rate of CBZ-E by changing the wax type.

(b) A relatively small amount (20% of tablet weight) of a wax was enough to affect the release rate dramatically.

1.2c TEMPERATURE DEPENDENCE OF THE RELEASE RATE

The results described above suggest that there should be a very significant influence of the dissolution medium temperature on a release rate. In order to evaluate this influence a series of dissolution tests was carried out. The dissolution conditions remained as before except that the dissolution medium temperature was set at 34°C, 35°C, 36°C, 37°C, 38°C and 40°C respectively. This temperature spectrum covered all the melting ranges from the lower limit of the lowest-melting wax to the upper limit of the highest-melting wax. In each test all the five types of waxes were used. It is important to note that in an attempt to evaluate possible release mechanisms and in order to achieve maximal uniformity of the dissolution conditions, all tablets were blocked with the help of Parafilm® and special rubber fits, so that only the upper flat (planar) side of the tablet was exposed to the dissolution medium throughout the experiments.

The results obtained in these experiments (Figs. 4-9) suggest several important conclusions:

- a) The release rate depends significantly on the dissolution medium temperature for all the wax types;
- b) At all temperatures the difference between the wax types remains similar, that is, waxes with higher melting range give slower dissolution rates.
- c) It has been noted that there was a possible difference in release mechanisms for low and high temperatures. Low temperatures produced release profile curves governed by the well-known Higuchi equation for diffusion-controlled planar system (W.I. Higuchi. *J. Pharm. Sci.* 56, 315-324, (1967)), while higher

temperatures provided apparent zero-order profiles. This phenomenon is discussed in the next part.

1.2d BEHAVIOR OF DIFFERENT WAX TYPES AT DIFFERENT TEMPERATURES. EVALUATION OF RELEASE MECHANISM

The data obtained from the series of dissolution tests described in the previous part, were grouped by wax types in order to determine the influence of the temperature on the release rate and the profile for each wax type.

All the wax types appeared to be strongly dependent on the dissolution medium temperature (see Fig. 10 for Witpsol H15 as an example). Such a dramatic influence of temperature on the release rate can be explained by the fact that the melting range of each wax was very close to the experimental temperatures. The lowest experimental temperature (34°C) was slightly below the lower limit of all melting ranges, and the highest (40°C) - above the upper limit of melting ranges of all the waxes. This fact explains why the difference between the release rates for different waxes was less significant at 34°C and 40°C (Figs. 4 and 9) than at intermediate (35°C, 36°C, 37°C and 38°C) temperatures.

However, the most interesting feature of the release profiles obtained, was the fact that at low temperatures the release was governed by the Higuchi equation while at high temperatures the release rate appeared to be apparently zero-order.

The Higuchi equation describes drug release from a planar, insoluble matrix system in which the rate-determining process is diffusion. This is given by equation (1):

$$Q = \left[\frac{D\varepsilon}{\tau} (2A - \varepsilon C_s) C_s t \right]^{1/2} \quad (1)$$

where Q is the amount of drug released per unit area of the disk exposed to the dissolution medium (in our case all tablets had the same exposed area);

D is the diffusion coefficient of the drug in the solvent;

ε is the porosity of the matrix;

τ is the tortuosity of the matrix;

A is the concentration of solid drug in the matrix (load);

C_s is the solubility of the drug in the solvent;

t is time.

The equation (1) can be reduced to the following:

$$Q = Kt^{1/2} \quad (2)$$

where

$$K = \left[\frac{D\varepsilon}{\tau} (2A - \varepsilon C_s) C_s \right]^{1/2}$$

which means that the amount released should be linearly proportional to the square root of time.

Additional mathematical treatment is needed in order to distinguish this mechanism from other possible mechanisms. Differentiation of equation (2) produces equation (3):

$$\frac{dQ}{dt} = \text{rate} = \frac{K^2}{2Q} \quad (3)$$

which indicates that the rate will be inversely proportional to the amount released, Q .

Further confirmation of the Higuchi mechanism can be obtained by logarithmic transformation of equation (3), yielding equation (4):

$$\log Q = \log K + \frac{1}{2} \log t \quad (4)$$

which predicts that a plot of $\log Q$ versus $\log t$ must give a straight line with a slope of $1/2$.

The mathematical treatment described above was applied to the data obtained in the dissolution experiments described above.

It was noted that none of the waxes gave a straight line (zero-order) dissolution profile at 34°C (Fig. 4). It was assumed that since this temperature was slightly lower than the melting range of all the waxes, the diffusion-controlled release mechanism (the Higuchi equation) may be applicable. Mathematical treatment confirmed this assumption. Figure 11 shows that the amount released plotted as a function of a square root of time yielded apparently straight lines for all the wax types at 34°C.

The calculated release rate (in mg per hour, Fig. 12) was proportional to the reciprocal amount released, as predicted by equation (3).

Finally, log of the amount released plotted as a function of log of time yielded straight lines with slopes very close to 1/2 (0.55 - 0.60) for all the waxes, as predicted by equation (4) (Fig. 13).

These results suggest that at 34°C the release process was indeed governed by the Higuchi law.

On the other hand, at 37°C and higher (especially at 40°C, see Fig. 9) the release profiles (at least for the low-melting waxes) yielded apparently straight lines, that is, zero-order release. Fig. 14 illustrates how at 37°C the highest-melting wax (Witepsol H37) still corresponded well to the Higuchi equation while the lower-melting waxes produced curves progressively deviating from the straight line, when plotted as a function of time square root. Obviously, at some point between the zero-order and the square root profiles either a combination of the two takes place or some kind of intermediate release mechanism appears.

On the basis of the data obtained in the experiments described above it is concluded that the low-melting waxes with melting ranges close to the body temperature can be used as an inactive ingredient for sustained release formulations. The relative required amount (20% w/w) of wax is very small compared to amounts usually used in matrix-type sustained release formulations, which allows loading of higher dosages.

The control of the release rate can be achieved by use of waxes with slightly different melting ranges.

The obtained results show that low-melting waxes are very attractive for a simple design of matrix-type formulations, providing zero-order release profiles.

Example 2: Pharmacokinetic studies in dogs

2.1 Carbamazepine 10, 11 epoxide

CBZ-E was administered to dogs as follows:

- 1) Intravenous administration of 250 mg in solution (n=3)
- 2) 250 mg were filled in hard gelatin capsules (n=3)
- 3) 250 mg granulated with 20% (of total wt) Witepsol H-37, and compressed to tablets (n=2). The tablets were enteric coated.

The CBZ-E plasma levels following i.v. administration and the two oral formulations are illustrated in Figure 15.

The following Table II summarizes the pharmacokinetic parameters (Gibaldi and Perrier, *Pharmacokinetics*, Marcel Dekker, Inc., New York, 1982, pp 33-40) derived from these profiles.

Table 1
Dissolution of CBZ-E as powder and from Wilepsol H115

| Hours | Vessel 1 (%) | Vessel 2 (%) | Vessel 3 (%) | Hours | Vessel 4 (%) | Vessel 5 (%) | Vessel 6 (%) |
|-------|-----------------|-----------------|-----------------|--|-----------------|-----------------|-----------------|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0.75 | 6.1 | 4.17 | 5.14 | 0.75 | 47.4 | 40.9 | 37.6 |
| 1.25 | 9.04 | 6.5 | 7.63 | 1.25 | 59.2 | 52.5 | 47.1 |
| 1.75 | 12.7 | 8.05 | 10.68 | 2.25 | 74.0 | 68.7 | 63 |
| 2.75 | 19.6 | 12.16 | 16.61 | 3.25 | 89.1 | 83.7 | 78.1 |
| 3.75 | 25 | 15.57 | 22.52 | 5.25 | 108 | 99.6 | 94.3 |
| 4.75 | 31.5 | 20.11 | 28.3 | 7.25 | 110.6 | 107.8 | 106 |
| 5.75 | 39.9 | 23.1 | 33.8 | Vessel 1 - 348.2mg "tablet" in water (paddle) | | | |
| 6.75 | 47.1 | 26.58 | 38.33 | Vessel 2 - 335.4mg "tablet" in buffer (basket) | | | |
| 7.75 | 53.7 | 27.72 | 43 | Vessel 3 - 335.3mg "tablet" in buffer (paddle) | | | |
| 8.75 | 58.4 | 28.24 | 45.6 | Vessel 4 - 111.3mg of CBZ-E powder in capsule (water, paddle) | | | |
| 9.75 | 62.9 | 28.75 | 48.1 | Vessel 5 - 104.9mg of CBZ-E powder in capsule (buffer, paddle) | | | |
| 10.5 | 65.7 | 28.79 | 48.63 | Vessel 6 - 243.3mg of CBZ-E powder in capsule (buffer, paddle) | | | |

Experiment conditions: 37C, 900ml, 75rpm

Buffer: 0.30g of citric acid + 2.2g Na₂HPO₄·2H₂O + 0.1ml of phosphoric acid in 900ml of water (pH=6.8)

The "tablet" consists of CBZ-E powder and Wilepsol H115 (1:1)

Table II

| Parameter | <i>i.v. bolus</i> | immediate Rel. capsules | Witepsol H-37 tabs |
|--------------------------|--------------------|----------------------------|-----------------------|
| V | 25.33 (+4.03) | 29.83 (+6.45) | 73.43 |
| k_{01} | | 0.2808 (+0.032) | 2.3945 |
| k_{10} | 0.3166 (+0.067) | 0.2762 (+0.037) | 0.1185 |
| AUC (=D/V/ k_{10}) | 51.97 (+11.09) | 32.05 (+10.56) | 29.29 |
| $t_{1/2} k_{01}$ | | 2.48 (+0.27) | 0.31 |
| $t_{1/2} k_{10}$ | 2.26 (+0.55) | 2.54 (+0.34) | 5.97 |
| Tmax | | 3.62 (+0.44) | 1.37 |
| Cmax | 16.08 (+2.79) | 3.22 (+0.74) | 2.92 |

2.2 Monohydroxycarbazepine (MHD)

2.2.1 Study I

MHD was administered as follows:

- 1) Intravenous administration of 400 mg in solution (n=6)
- 2) 400 mg were filled in hard gelatin capsules (n=3)
- 3) 400 mg granulated with 25% (of total wt) Witepsol W-31, and compressed to tablets (n=3)
- 4) 400 mg granulated with 28% Witepsol H-37, and compressed (n=1)
- 5) 400 mg granulated with 25% Myvacet 5-07, and compressed (n=1)
- 6) 400 mg granulated with 25% Myvacet 7-07, and compressed (n=1)
- 7) 400 mg granulated with 15% 1:1 Witepsol W-31/Myvacet 5-07, and compressed (n=1)
- 8) 400 mg granulated with 15% Myvacet 5-07, and compressed (n=1)

- 9) 400 mg granulated with 20% 1:1 Witepsol W-31/Myvacet 5-07, and compressed (n=1)

The MHD plasma levels following administration and the various oral formulations are illustrated in Figures 16-19.

The following Table III summarizes the pharmacokinetic parameters derived from these profiles.

Table III

| Parameter | <i>i.v. bolus</i> | immediate Rel. capsules | Witepsol H-37 tabs | Witepsol W-31 tabs |
|--------------------------|---------------------|----------------------------|-----------------------|--------------------------|
| V | 25.27 (+3.95) | 25.80 (+10.36) | 23.34 | 34.23 (+10.80) |
| k_{01} | | 0.7597 (+0.6125) | 2.336 | 1.665 (+0.730) |
| k_{10} | 0.3295 (+0.0656) | 0.4130 (+0.0344) | 0.2420 | 0.2310 (+0.045) |
| AUC (=D/V/ k_{10}) | 50.19 (+9.35) | 40.60 (+11.02) | 70.67 | 53.55 (+8.25) |
| $t_{1/2} k_{01}$ | | 1.30 (+0.73) | 0.29 | 0.46 (+0.16) |
| $t_{1/2} k_{10}$ | 2.18 (+0.49) | 1.68 (+0.14) | 2.86 | 3.07 (0.55) |
| Tmax | | 2.04 (+0.77) | 1.08 | 1.46 (+0.36) |
| Cmax | 16.19 (+2.81) | 7.71 (+0.3.64) | 13.18 | 8.90 (+2.56) |

2.2.2 Study II

In another set of experiments the effect of pretreating the gastrointestinal tract by anticholinergic agent was checked. It should be noted that the gastrointestinal motility in dogs is higher compared to humans, therefore, depression of this action by anticholinergic agent can produce a more appropriate model of human oral absorption.

In these experiments MHD was administered as follows:

- 1) 400 mg MHD in capsules for immediate release (n=6)
- 2) 400 mg were MHD in tablets granulated with 25% Witepsol W3 (n=4)
- 3) same as in 2 but after the GI tract was pretreated with 30 mg of propantheline bromide after Yamakita et al, Biol. Pharm. Bull 18: 984-989, 1995

Fig 20 shows the results for this set of experiments. It is obvious that the gastrointestinal absorption of drugs from immediate release dosage forms is not influenced from the GI motility as much as the absorption from controlled release drug delivery systems.

It can be seen from Fig. 20 that the low-melting wax in the low motility gut caused a flat plasma drug profile, suggesting that in an environment of low disintegrating forces, such as occur in the human GI, a more sustained release of the drug is obtained. The time to reach this flat part of the profile is apparently governed by the enhancement of drug absorption and the fact that the flat plasma-drug profile is achieved after only 2 hours (as the immediate release T_{max}) indicates a faster absorption characteristics.

Example 2 shows that the low-melting waxes increase the absorption of drugs through the intestinal wall into the blood circulation while reducing the rate of drug elimination from the body. The former property indicates that the waxes act as carriers to enhance drug absorption, and the latter implies on a sustained release manner of drug delivery.

Examples 1 and 2 demonstrate that the present invention is useful for:

- (a) administration of less amount of drug than is required by the conventional methods while still maintaining the same activity because of gastric and intestinal absorption enhancement.
- (b) loading more drug in smaller dispensing system (i.e., small tablet's size)
- (c) a sustained drug release wherein the required rate of drug release is obtained by the percent of wax present in the composition or by combination of waxes with different melting points, all of them, or at least one of them, in the range of 30° to 40°.
- (d) protecting low pH-sensitive molecules in the gastric fluid and protecting proteins and peptide drugs from being degraded by the proteolytic enzymes in the intestinal lumen. It should be noted that these kind of protection can allow targeting of drugs to the colon for treating colon-specific diseases or slow-release absorption in this organ.

CLAIMS

- 1) A pharmaceutical composition for oral administration comprising at least one active ingredient, and a low-melting wax or waxes, wherein the wax melting point temperature is in the range of 30°C to 40°C.
- 2) A pharmaceutical composition for oral administration according to claim 1 wherein said composition is applied as tablets or compressed tablets and is prepared by direct compression or by granulation process or by any conventional technique known in the art and said composition comprising, in addition any binder, glint, lubricant compound or any other excipient commonly-used in the art of tablets preparation.
- 3) A Pharmaceutical composition for oral administration according to claim 1 wherein said composition is applied as microspheres and is prepared by any technique known in the art and where said composition may contain, in addition to the components disclosed in claims 1 and 2 any surfactant.
- 4) A pharmaceutical composition according to claim 1 wherein the low-melting waxes are glycerides of long-chain fatty acids.
- 5) A pharmaceutical composition according to claim 1 wherein the low-melting waxes are selected from the series of Witepsol.
- 6) A pharmaceutical composition according to claim 1 wherein the concentration of the low-melting waxes is in the range from 0.1% to 80% by weight.

- 7) A pharmaceutical composition according to claim 1 useful for high drug-loaded systems.
- 8) A pharmaceutical composition according to claim 1 useful as a method for a sustained drug release wherein the required rate of drug release is obtained by a combination of waxes with different melting points, where at least one of them melts within the range of 30° to 40°.
- 9) A pharmaceutical composition according to claim 1 useful to protect low pH-sensitive molecules in the gastric fluid, or to protect proteins and peptide drugs from being degraded by the proteolytic enzymes in the intestinal lumen.
- 10) A pharmaceutical composition according to preceding claims substantially as described and illustrated hereinbefore.

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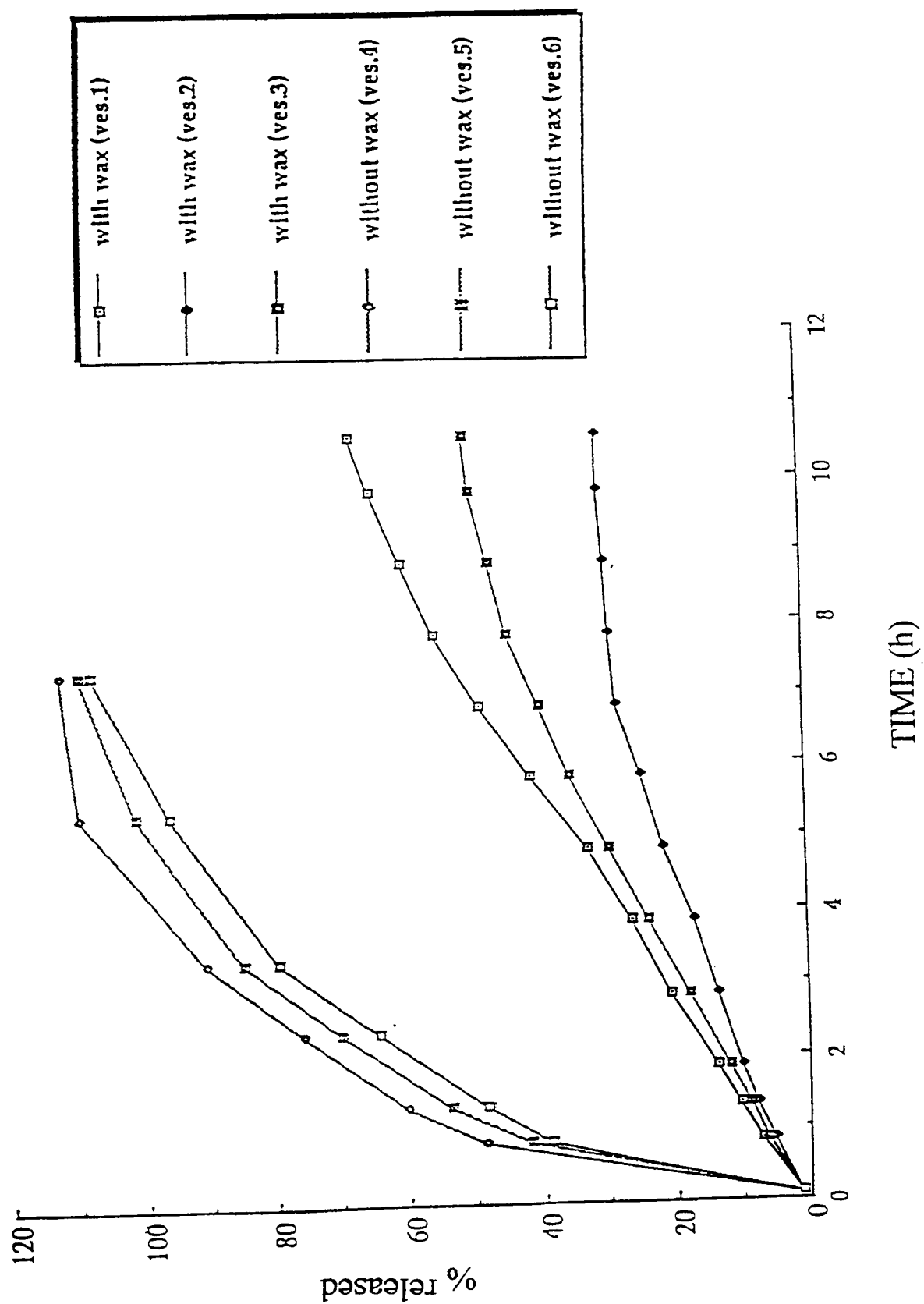


FIGURE 1

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Diss. of CBZ-E from various waxes

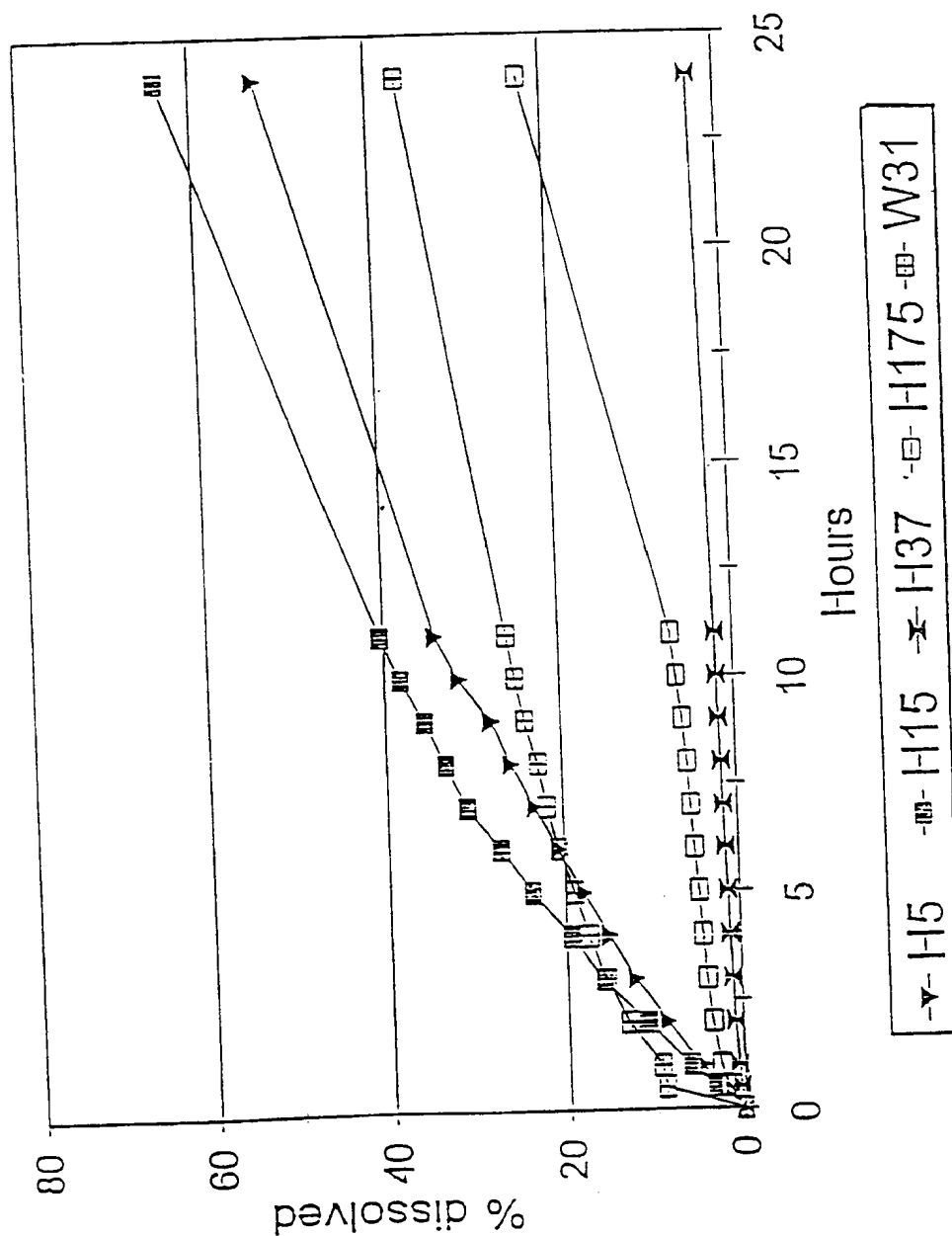


FIGURE 2

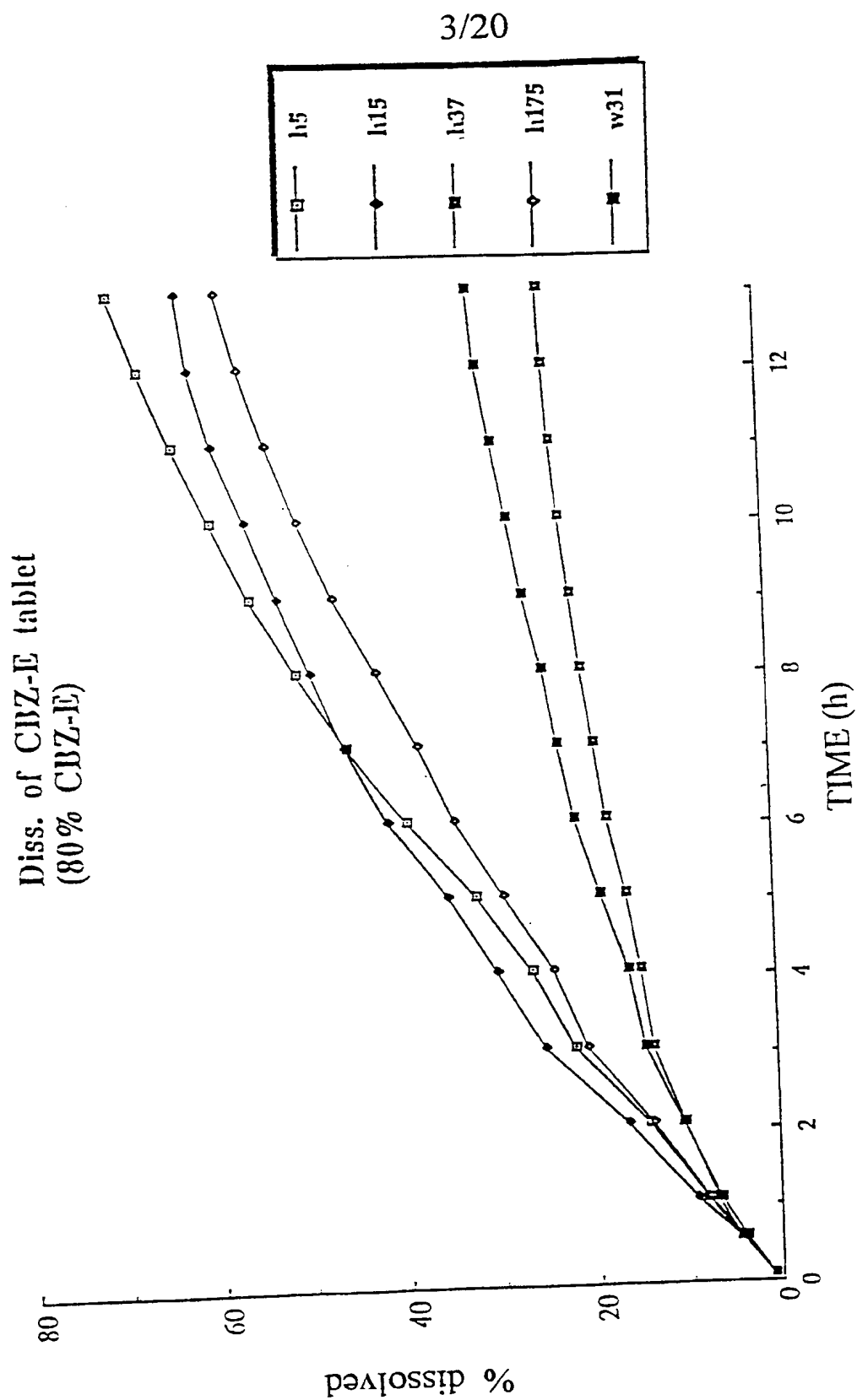


FIGURE 3

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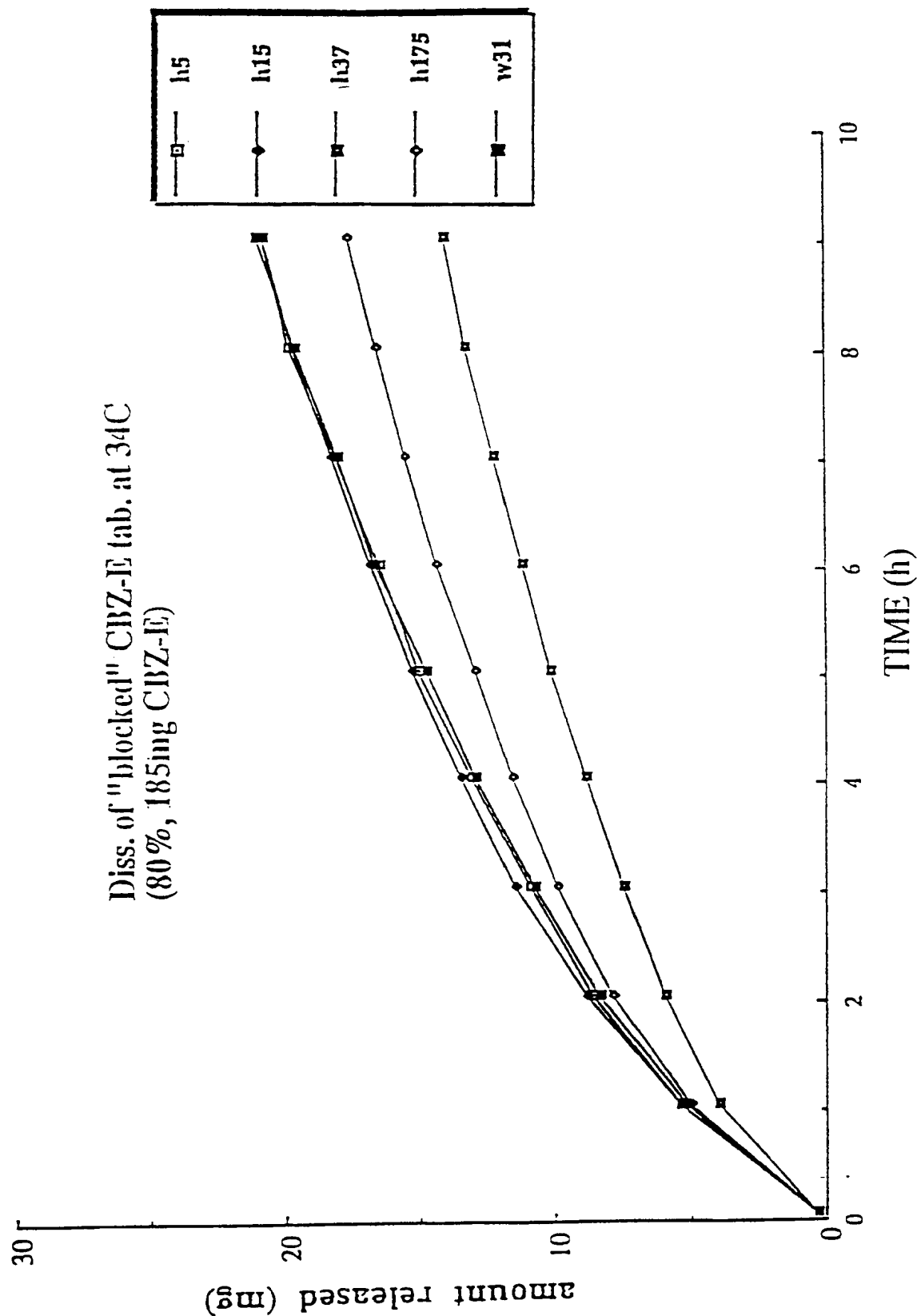


FIGURE 4

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Diss. of CBZ-E tablet (185mg,80% CBZ-E)
("blocked",35C)

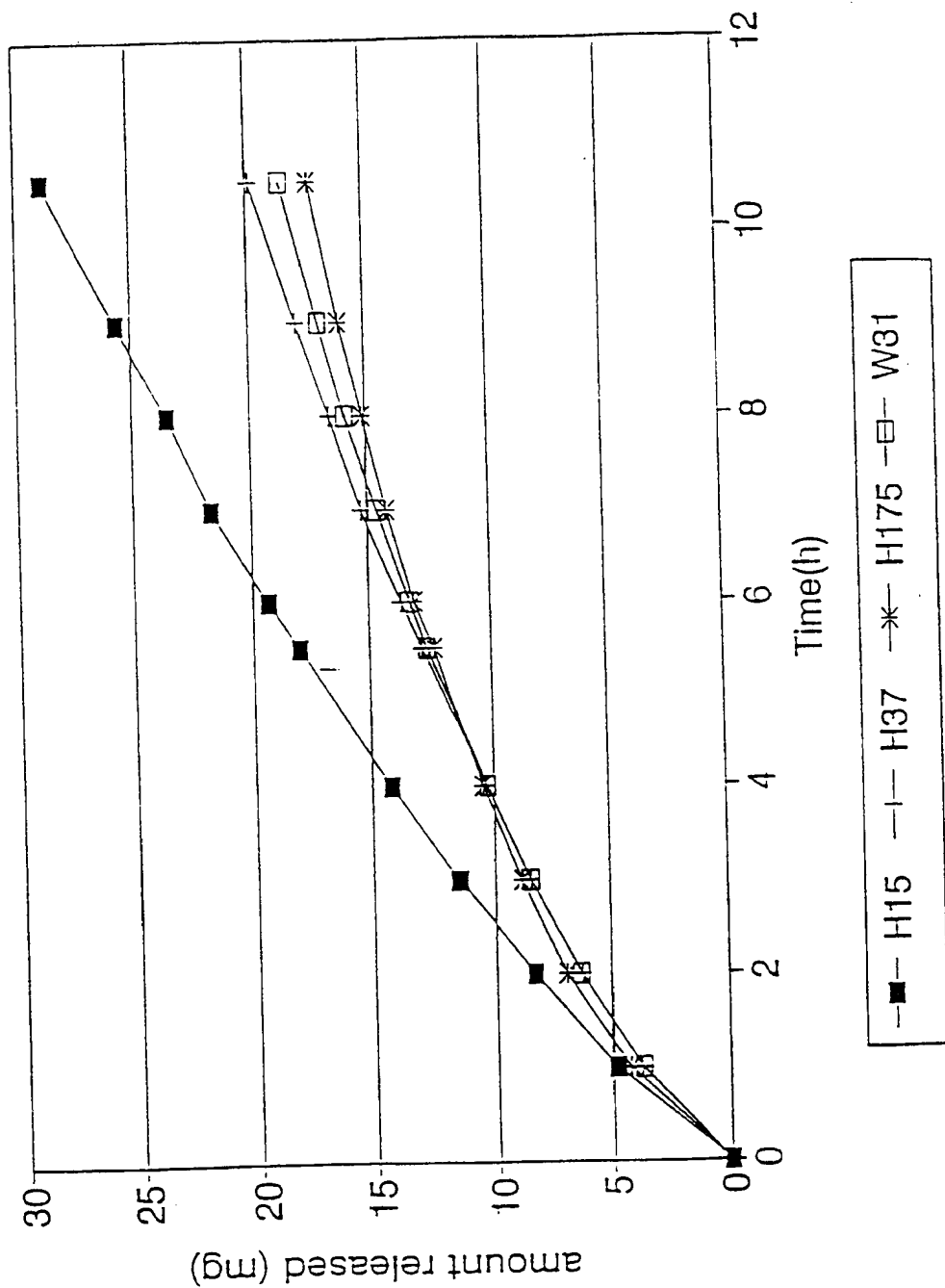
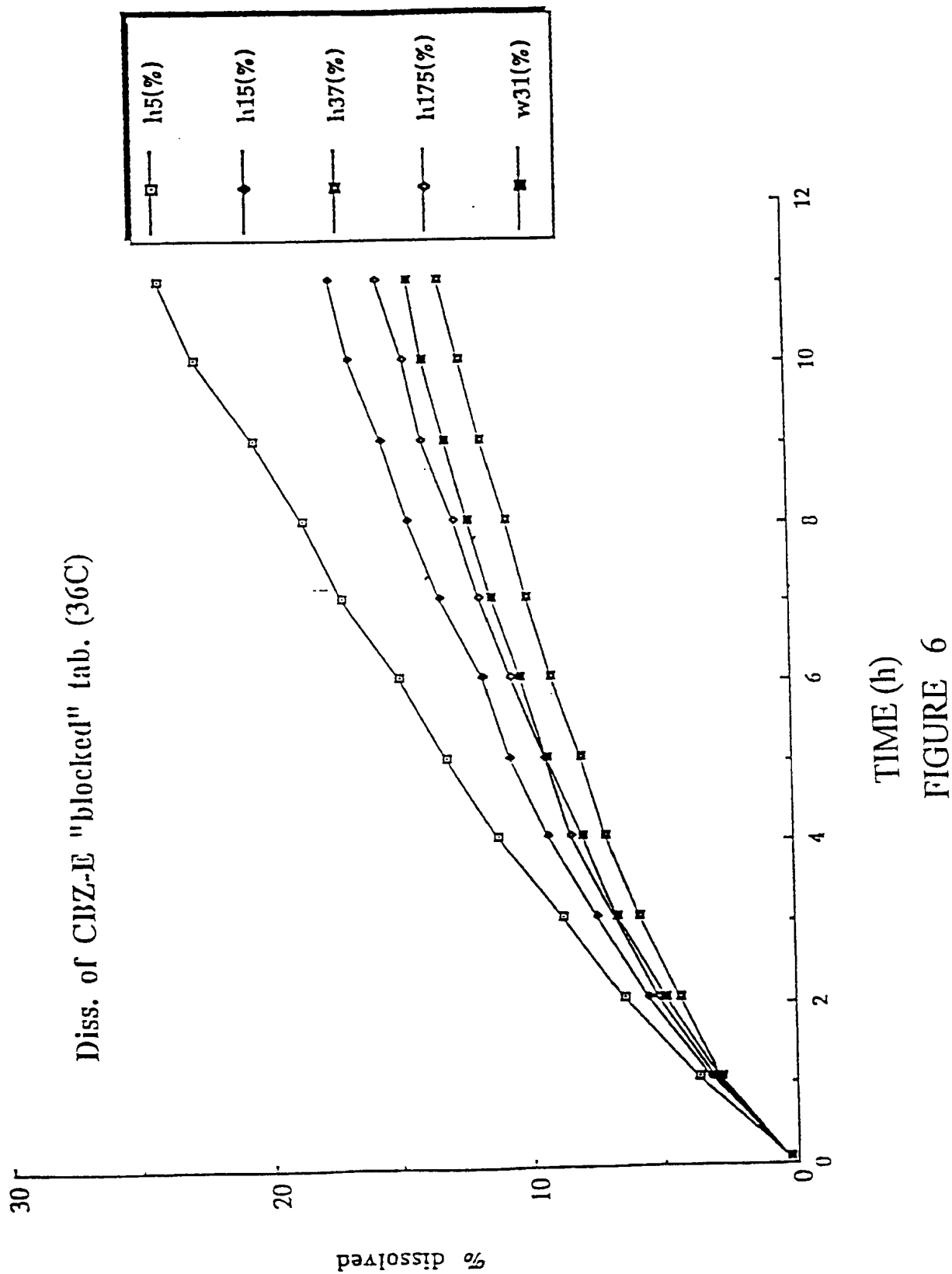


FIGURE 5

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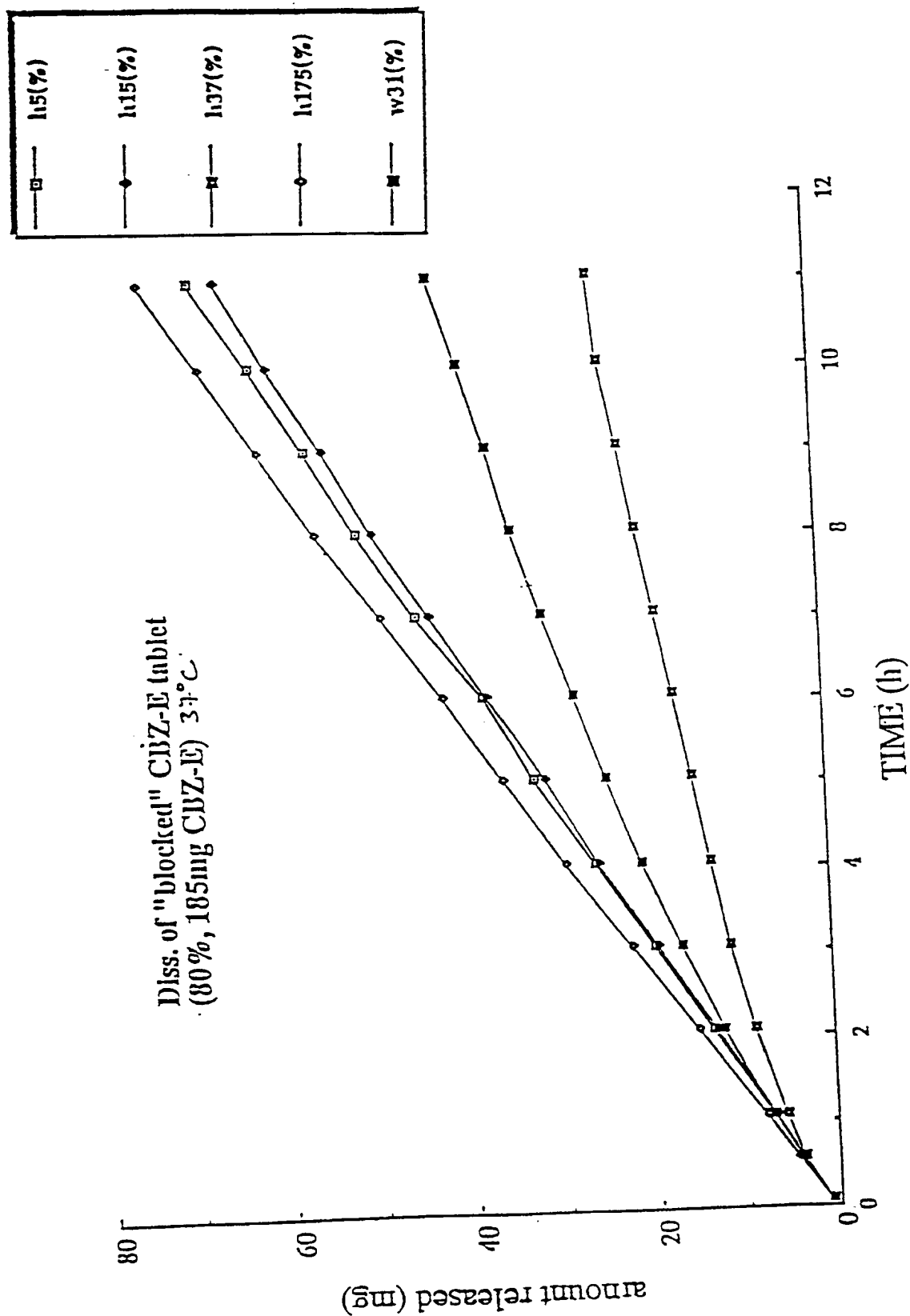


FIGURE 7

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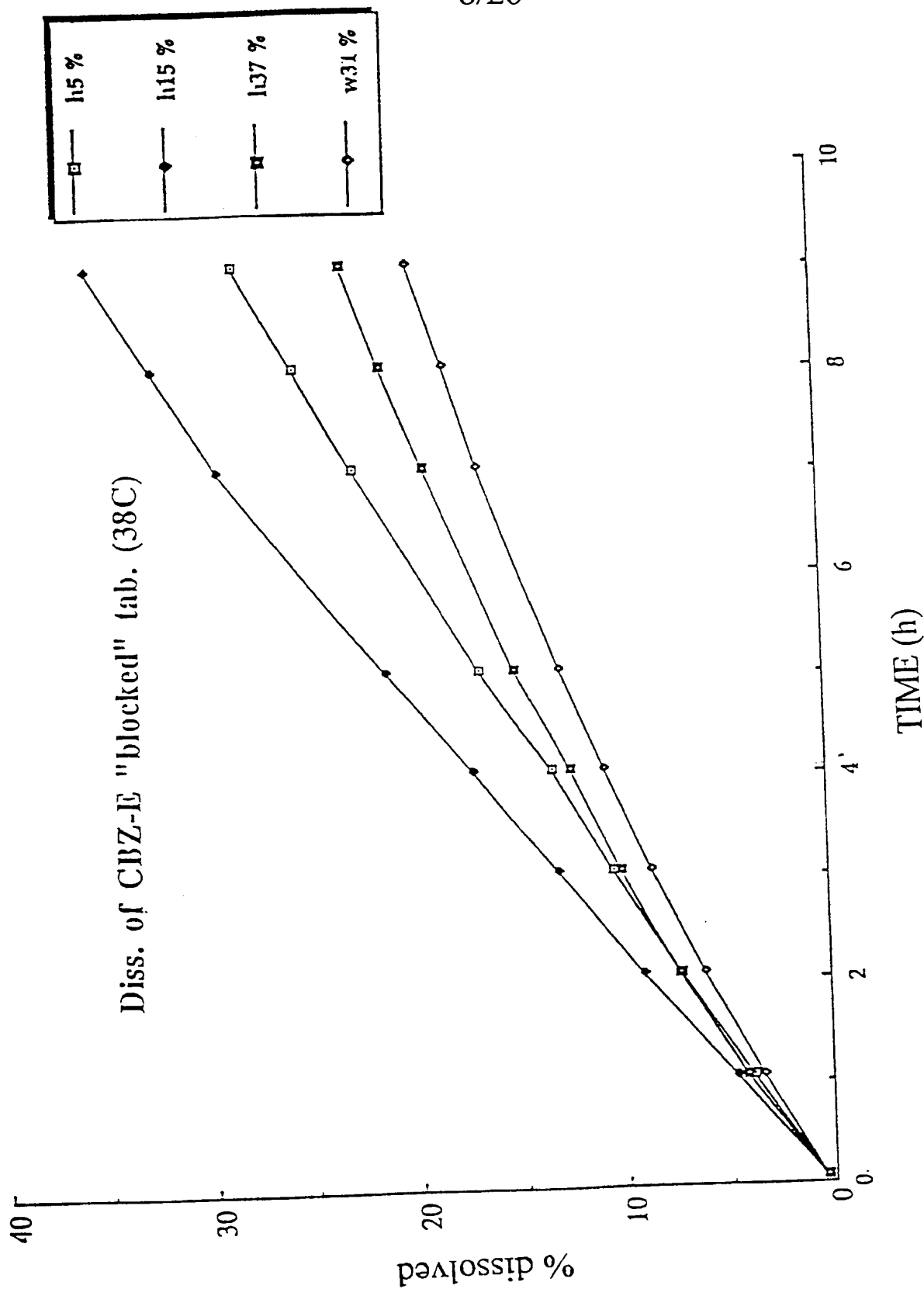


FIGURE 8

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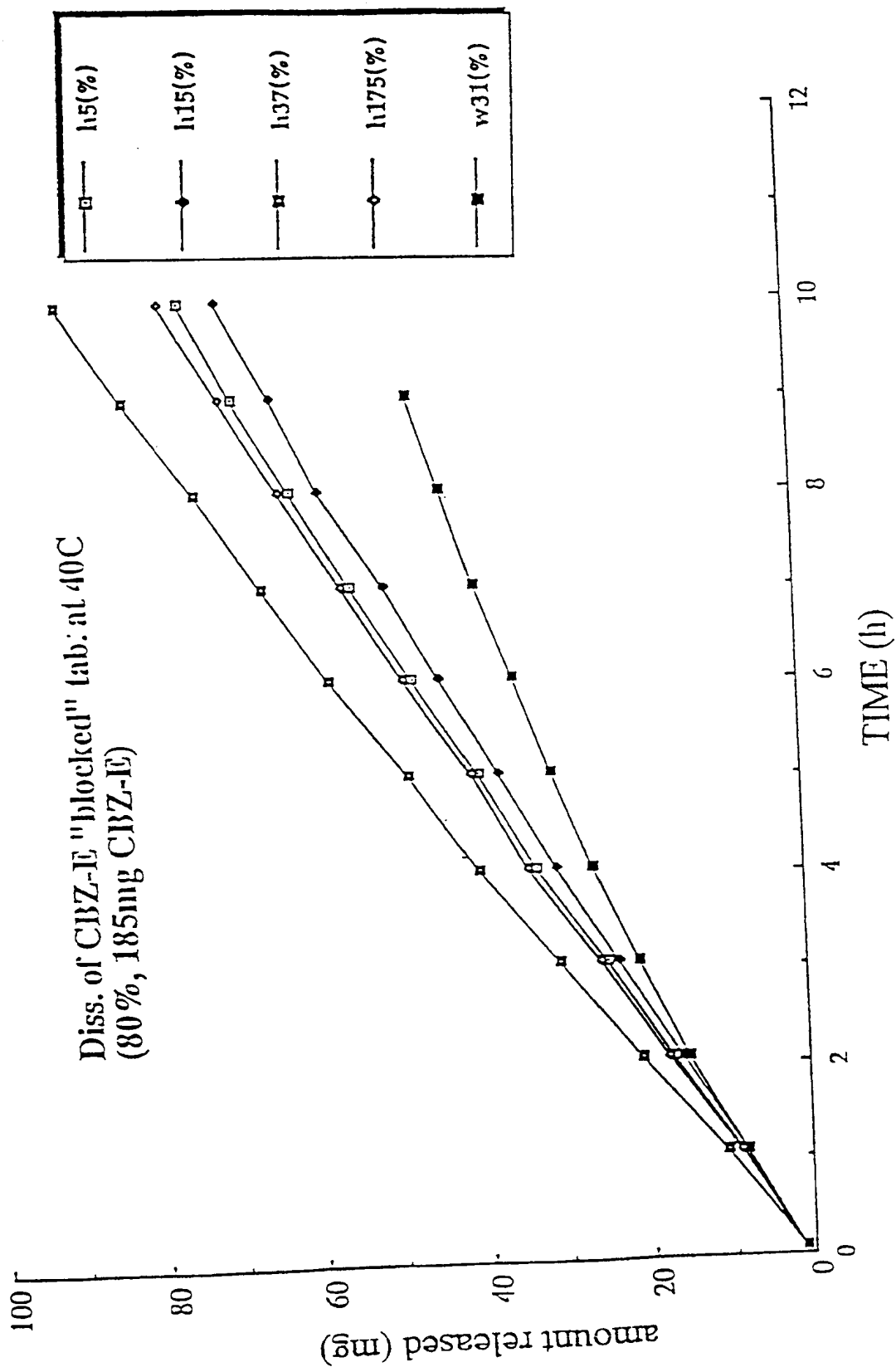


FIGURE 9

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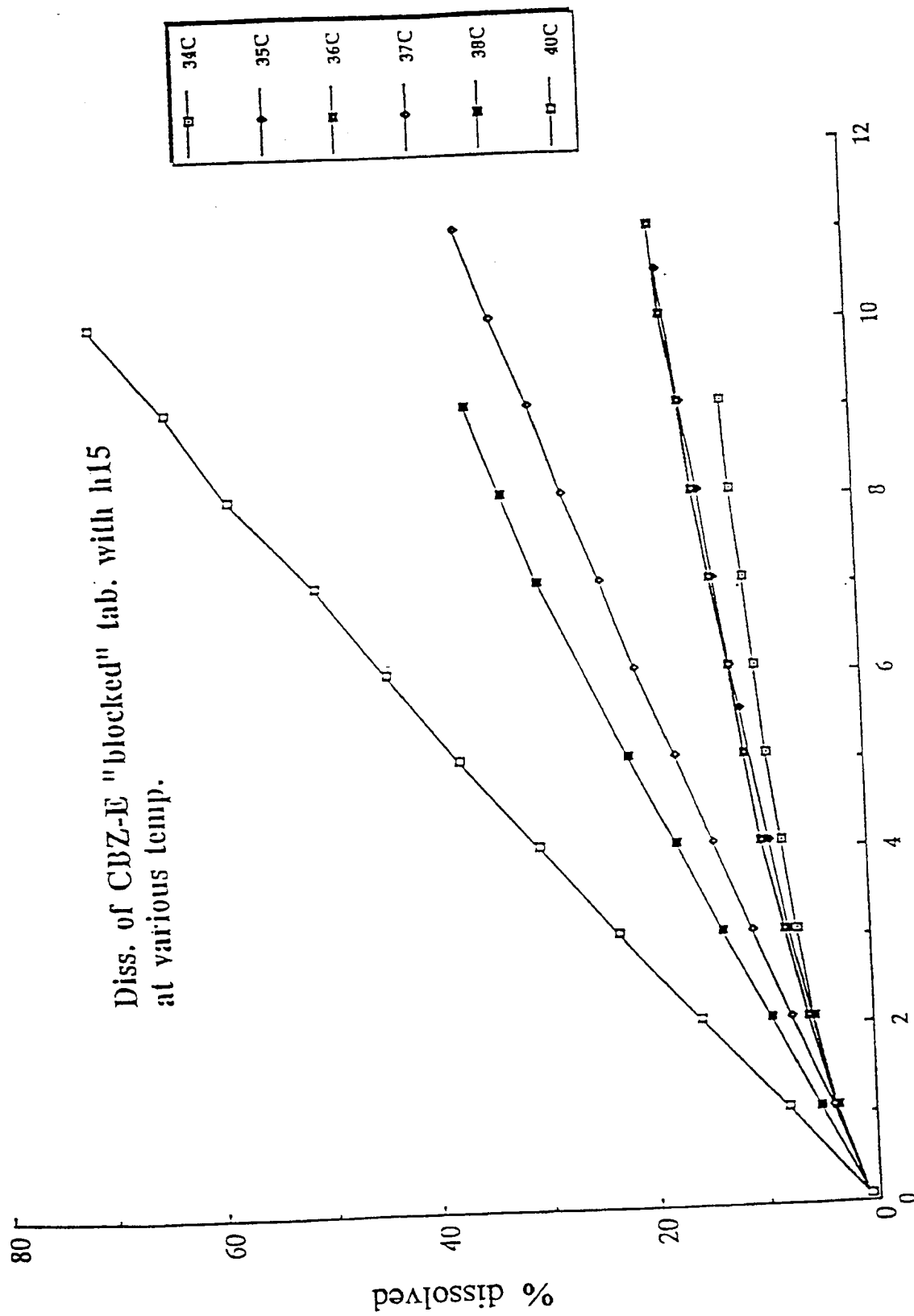


FIGURE 10

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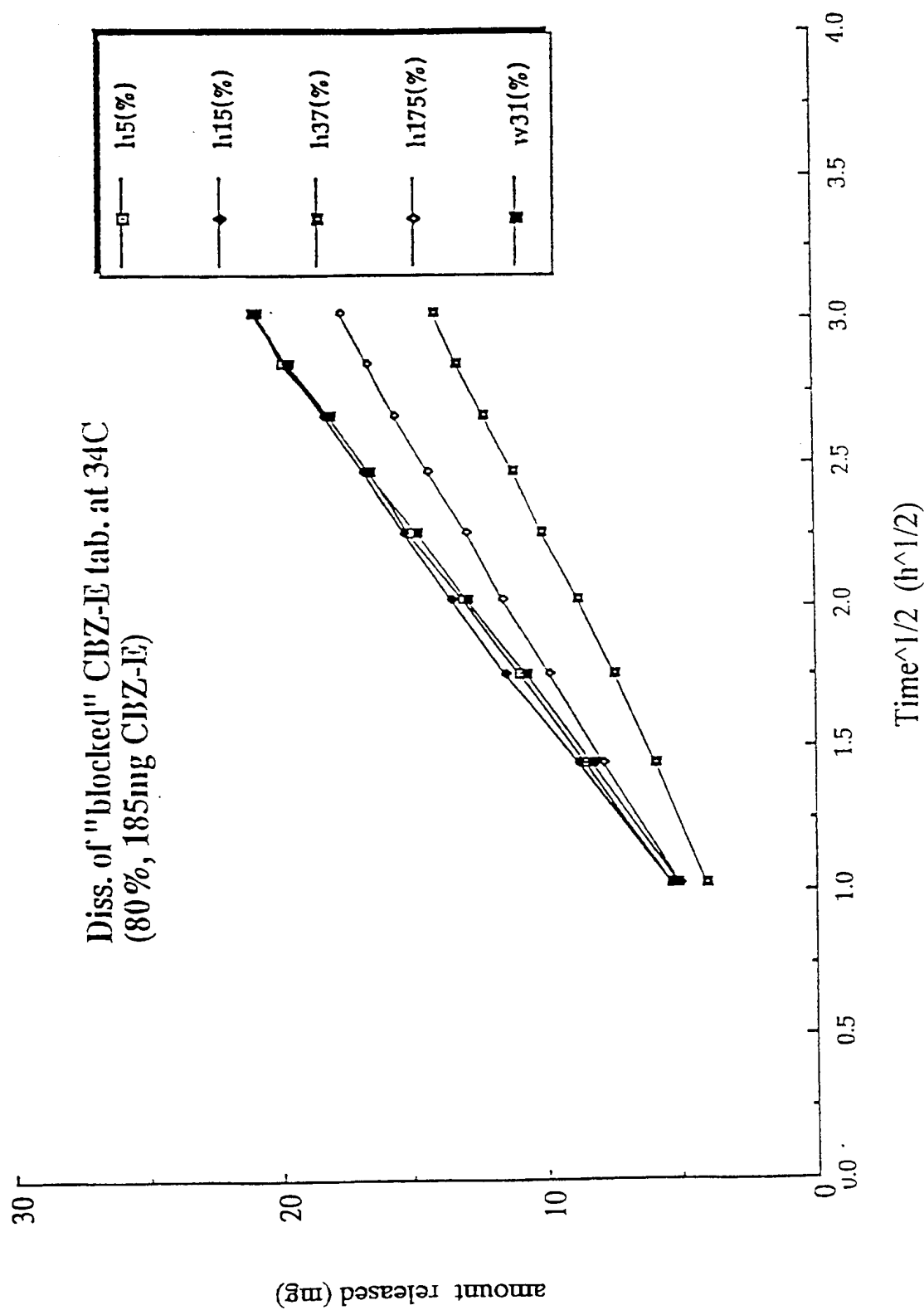


FIGURE 11

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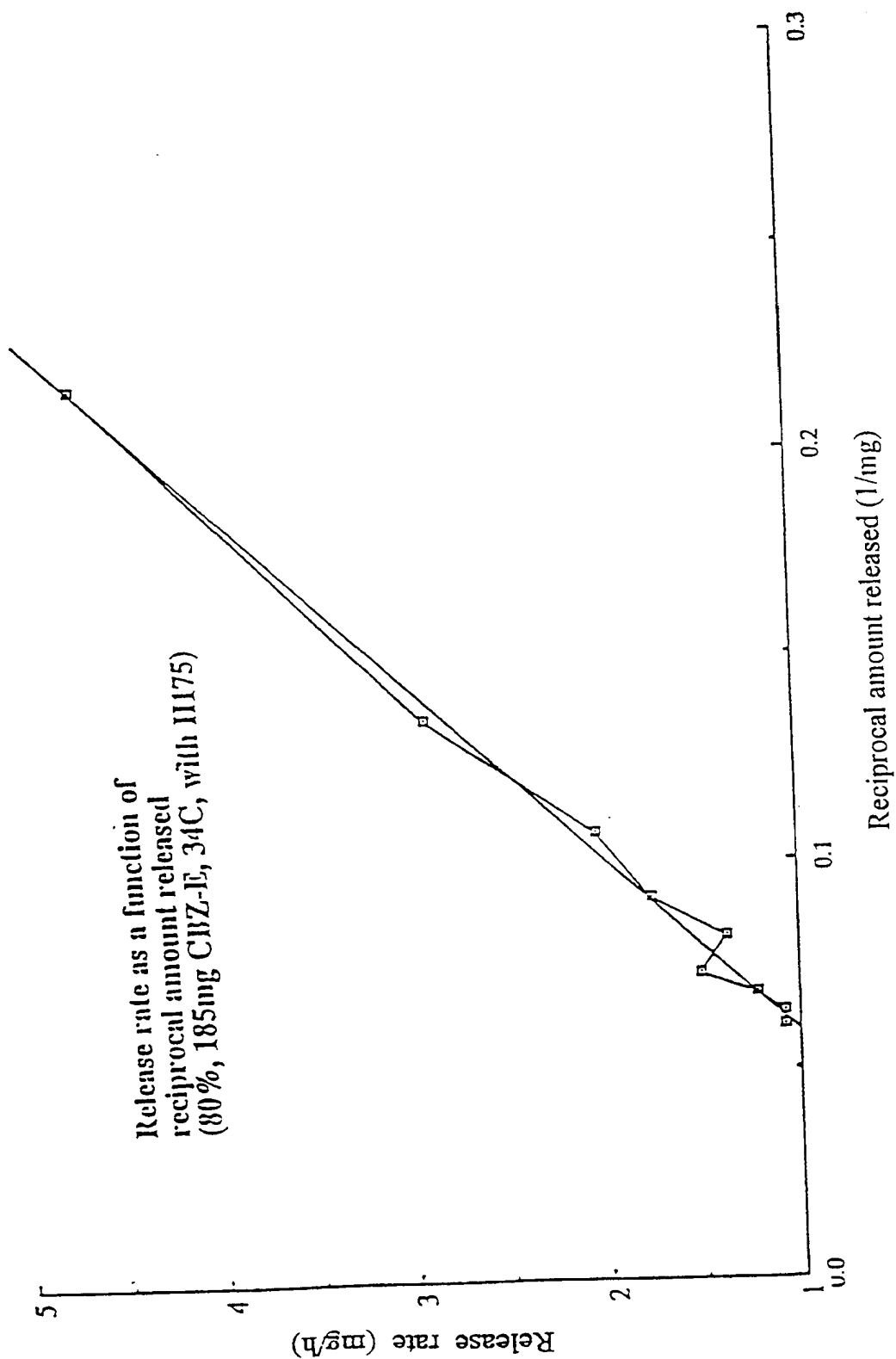


FIGURE 12

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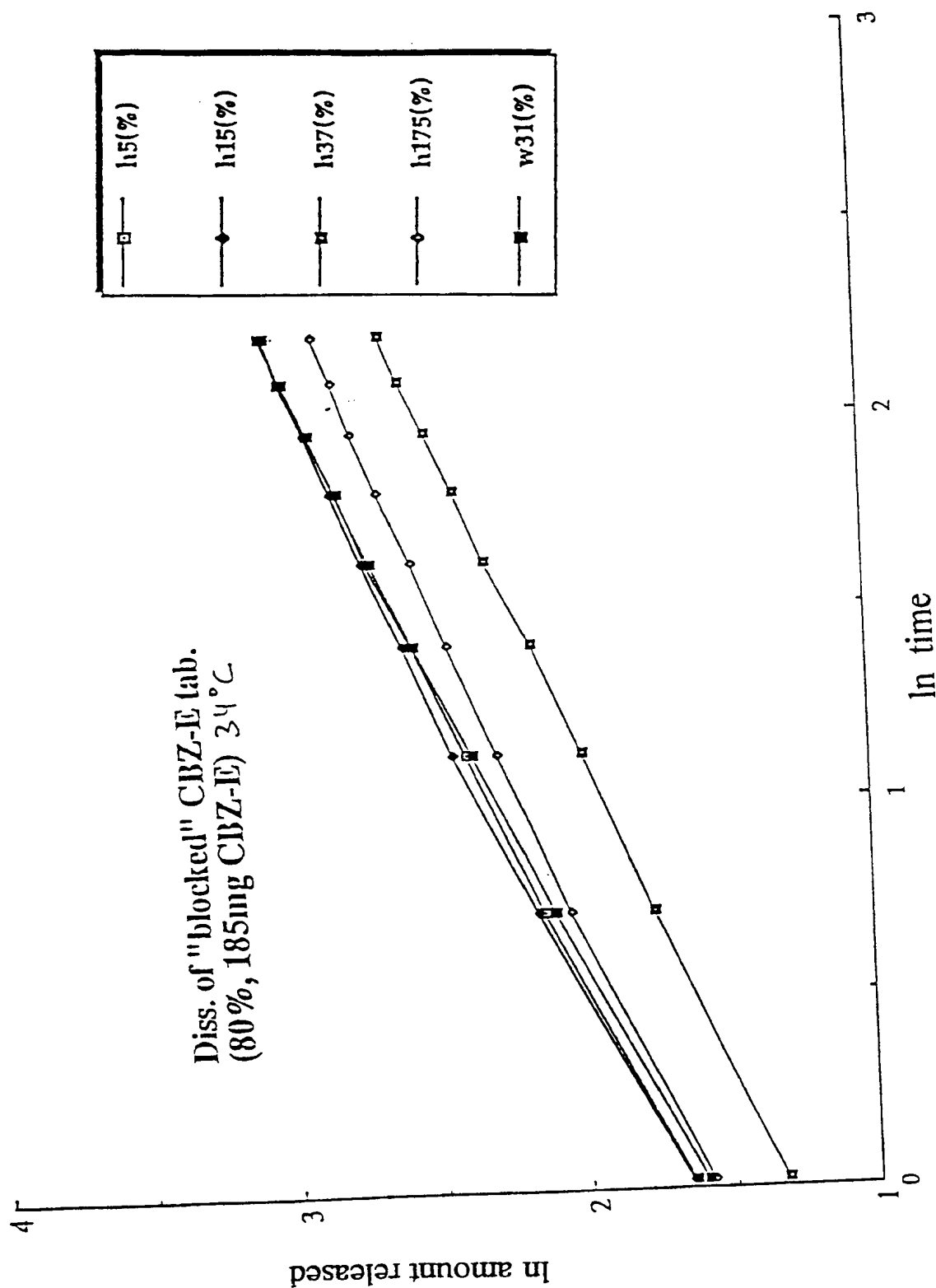
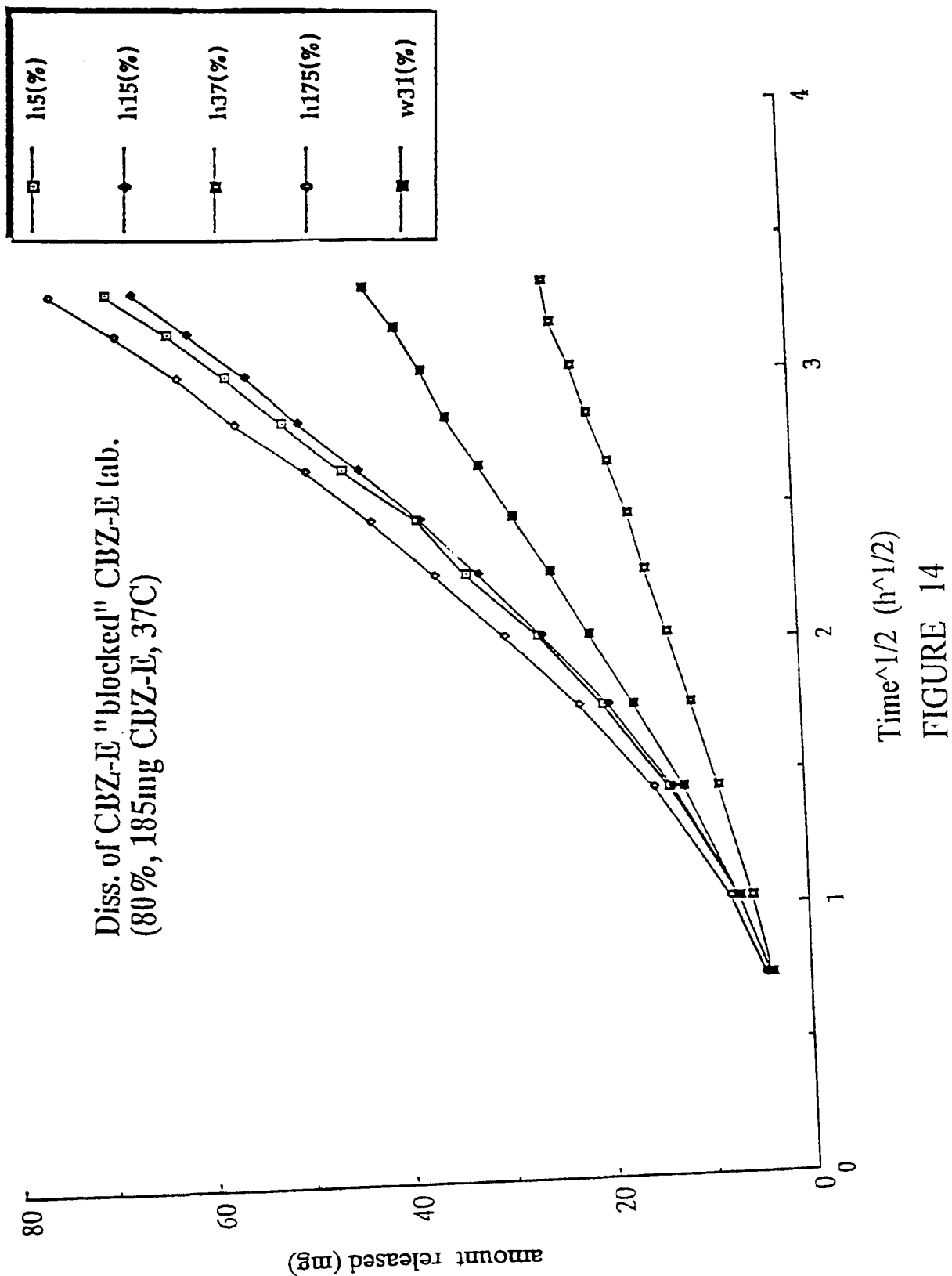


FIGURE 13



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CBZ-E Plasma levels
obtained after *i.v.* and oral administration to dogs (250 mg)

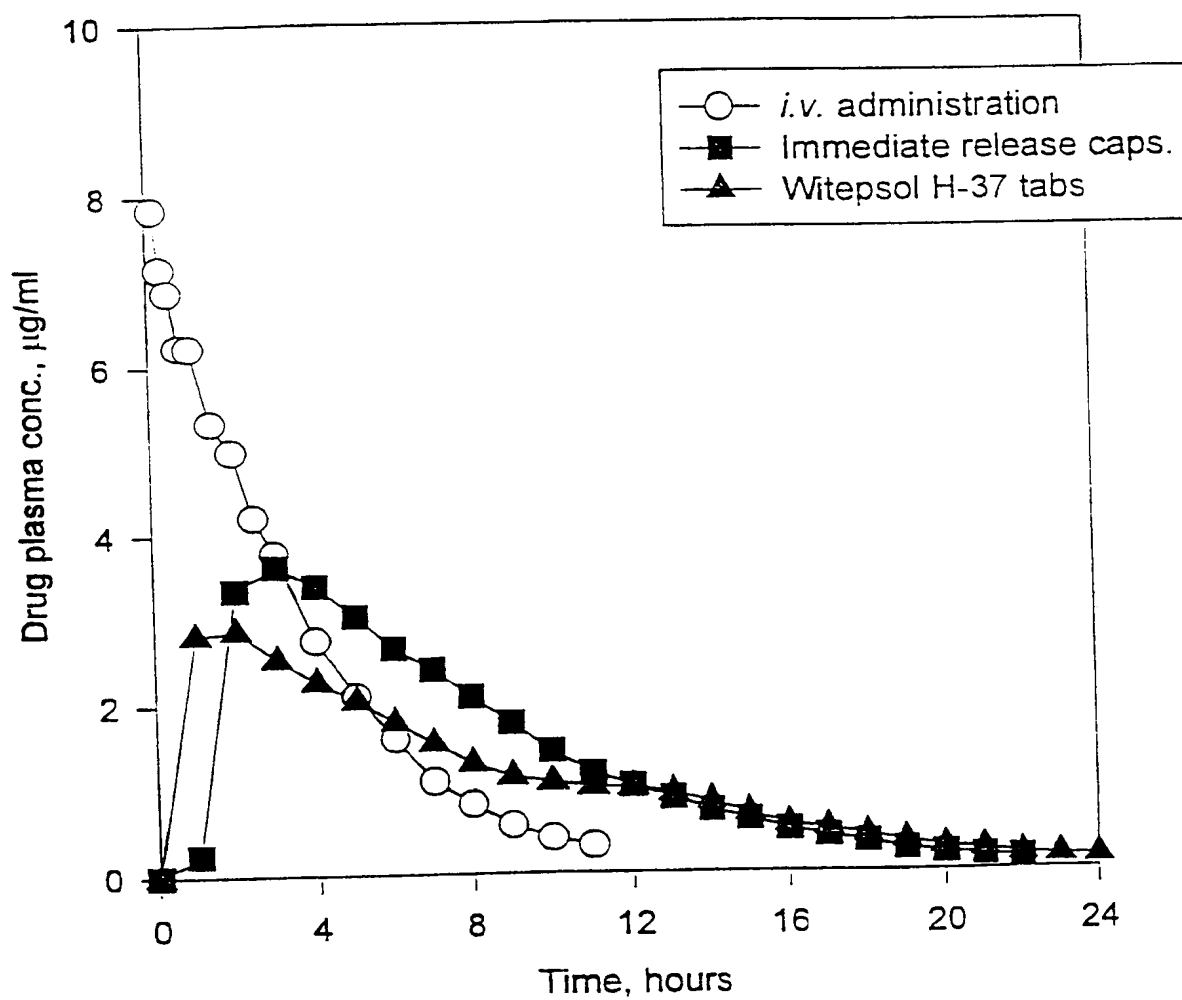


FIGURE 15

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MHD Plasma levels
obtained after *i.v.* and oral administration to dogs (400 mg)

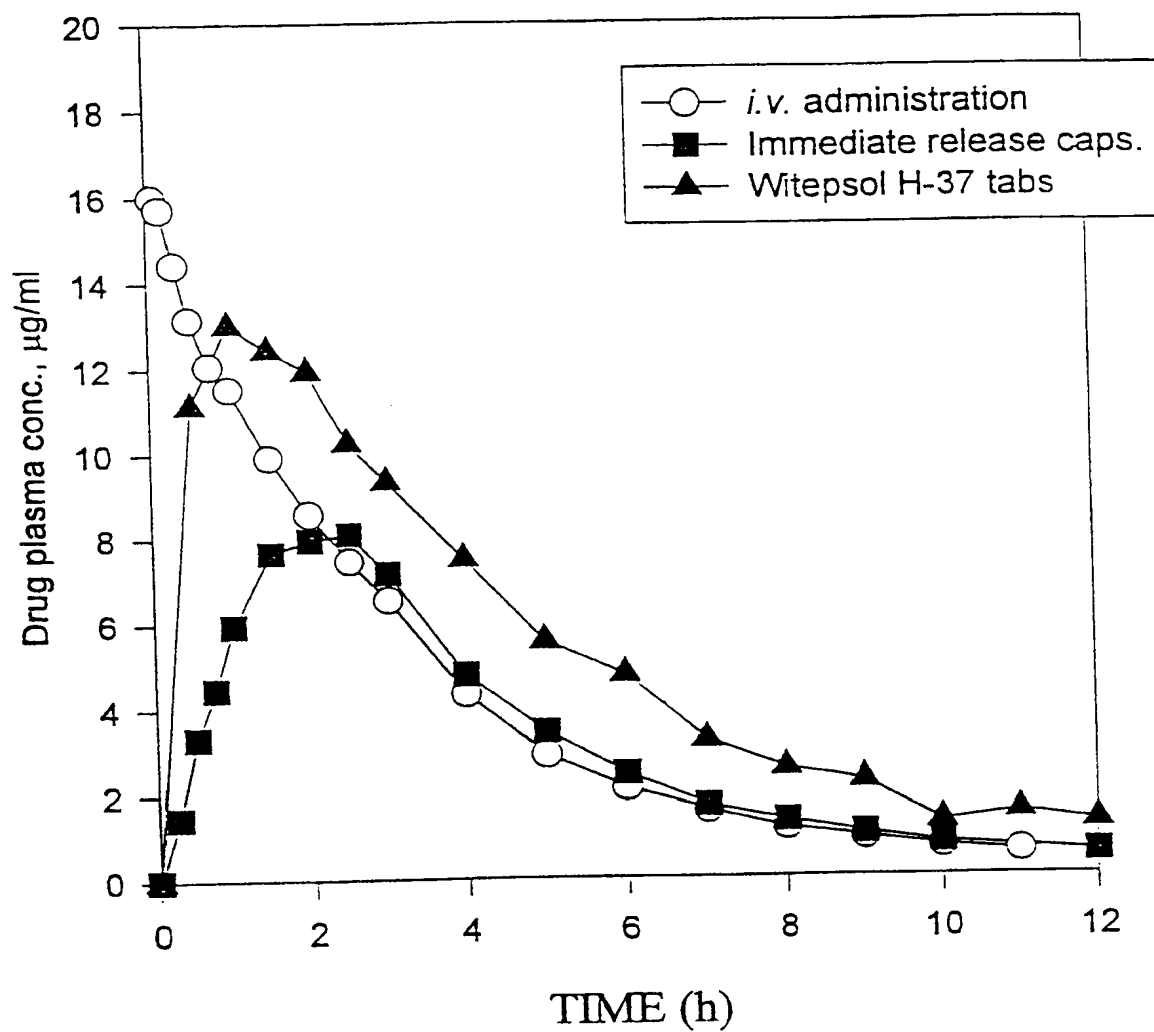


FIGURE 16

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MHD Plasma levels
obtained after *i.v.* and oral administration to dogs (400 mg)

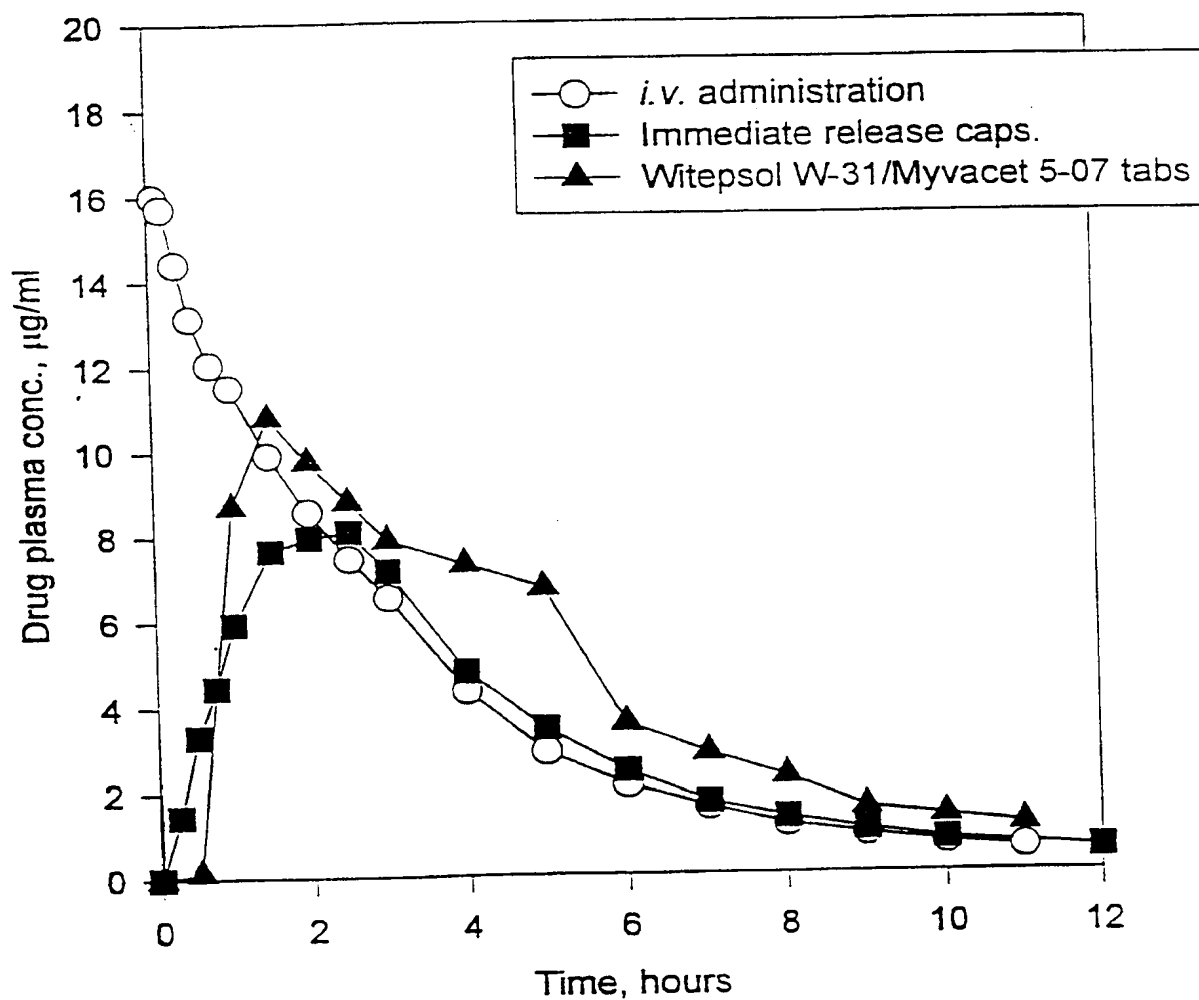


FIGURE 17

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MHD Plasma levels
obtained after *i.v.* and oral administration to dogs (400 mg)

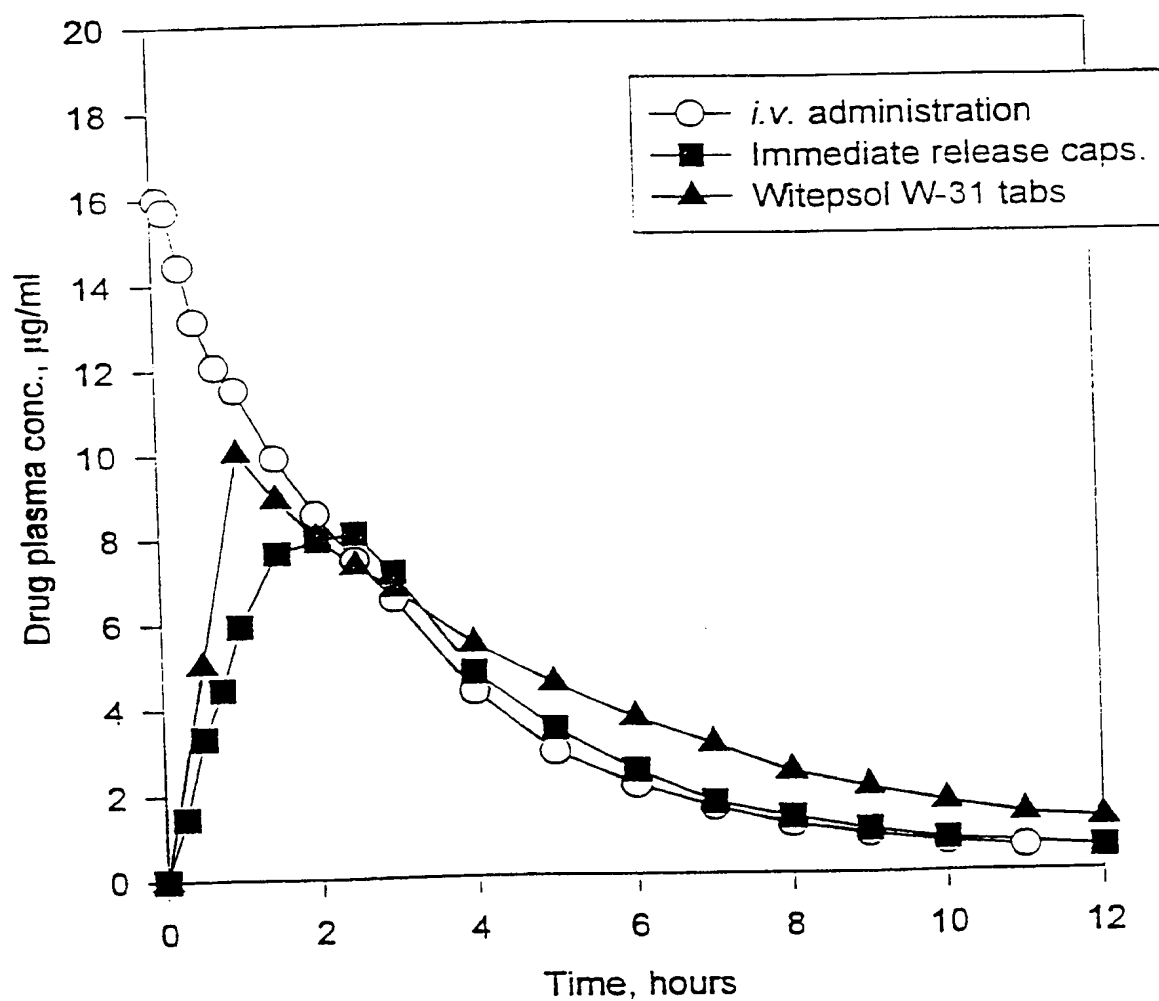


FIGURE 18

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MHD Plasma levels
obtained after *i.v.* and oral administration to dogs (400 mg)

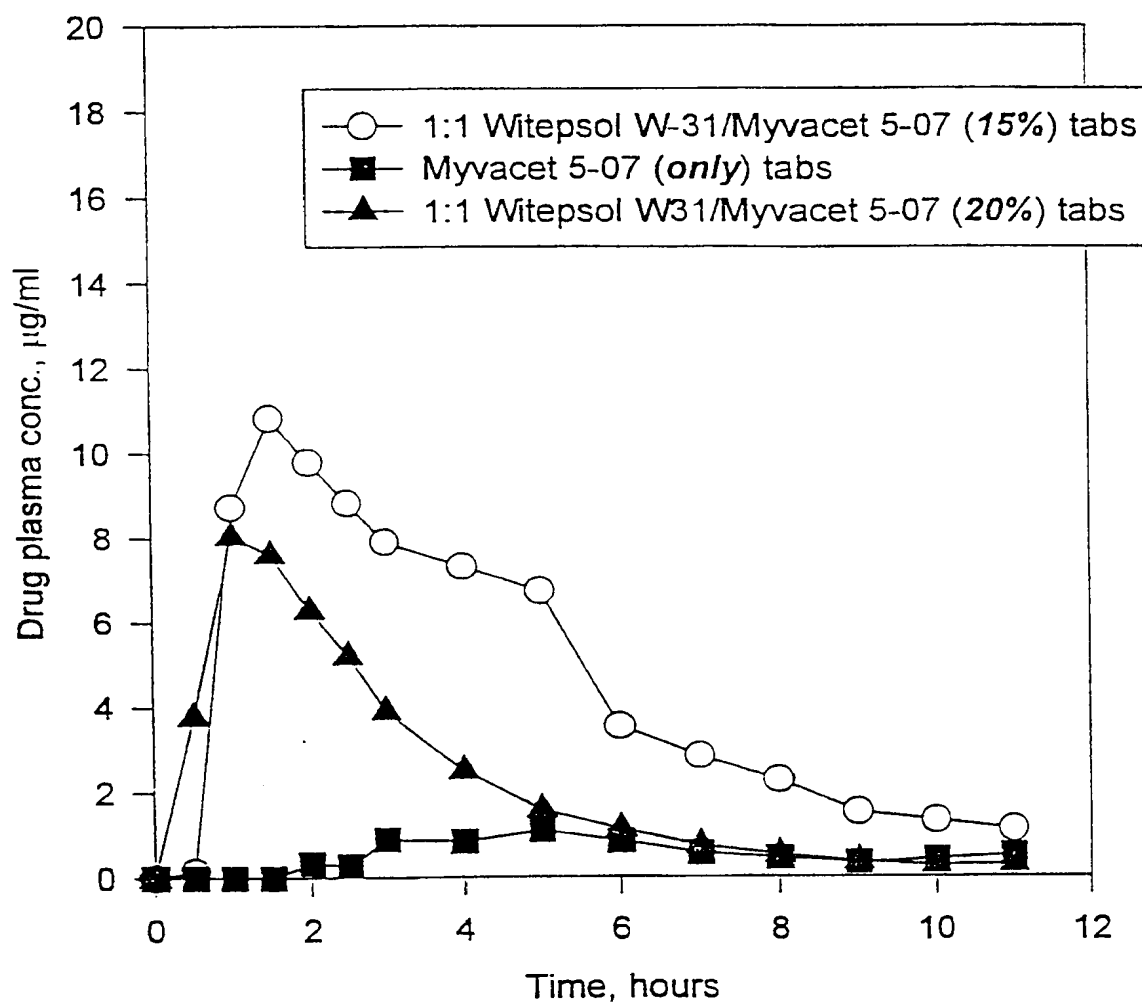


FIGURE 19

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Mean plasma MHD levels

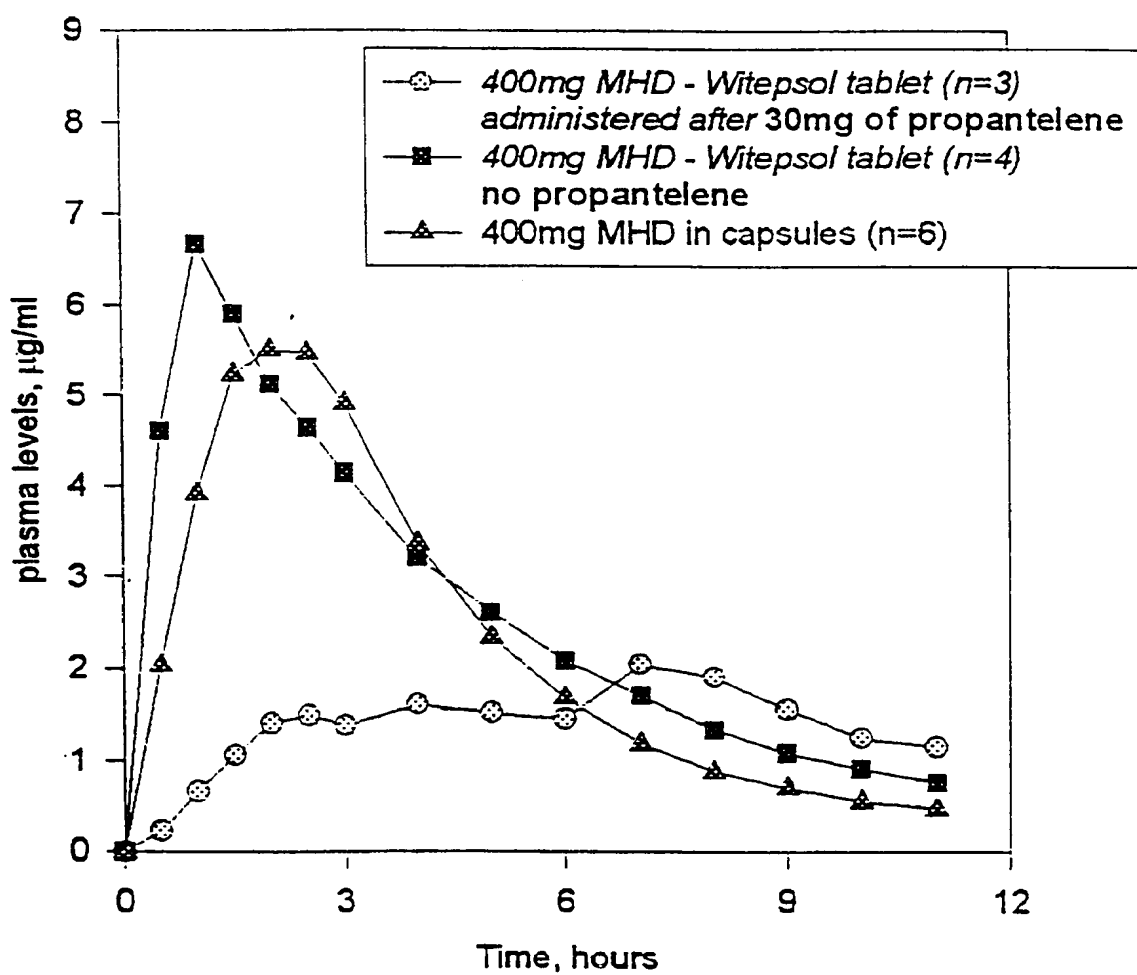


FIGURE 20

INTERNATIONAL SEARCH REPORT

Inte: onal Application No

PCT/IL 99/00365

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K47/06 A61K47/14 A61K9/20 A61K9/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

15 October 1999

Date of mailing of the international search report

26/10/1999

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| Y | column 9; example 15 ---- | 2,3 |
| X | EP 0 370 481 A (HOFFMANN LA ROCHE) 30 May 1990 (1990-05-30) | 1,4-10 |
| Y | page 12, line 1-25 page 13, line 30-50 ----- | 2,3 |

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